

**Except From:**  
**Diversity of Marine and Freshwater Algal Toxins**

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### Neurotoxic Shellfish Toxins

The occurrence of neurotoxic shellfish poisoning (NSP) has historically been limited to the west coast of Florida (Figure 3), where blooms of the dinoflagellate *Gymnodinium breve* initiate offshore and are subsequently carried inshore by wind and current conditions (20). Gulf of Mexico *G. breve* blooms are occasionally carried around the base of Florida by the Loop Current and northward by the Gulf Stream, resulting in red tides on the east coast of Florida and, in a single incident in 1987, as far north as North Carolina (21). In 1993, an unprecedented outbreak of shellfish toxicity in New Zealand resulted in the identification of additional *Gymnodinium* species (referred to as *Gymnodinium cf. breve*) which produce NSP-like toxins, (22). Recently, other fish killing flagellate species, *Chatonella marina*, *C. antiqua*, and *Fibrocapsa japonica*, and *Heterosigma akashiwo*, have also been reported to produce this class of polyether toxins (23,24,25).

The toxins responsible for NSP are a suite of ladder-like polycyclic ether toxins collectively called brevetoxins (PbTx, for *Ptychodiscus brevis*, more recently restored to its earlier taxonomic designation, *Gymnodinium breve*) (Figure 4). Brevetoxin congeners fall into two types based on backbone structure, the brevetoxin B backbone (type 1) and brevetoxin A backbone (type 2). The type 1 congeners are the most abundant in nature, with PbTx-2 and PbTx-3 being the most prevalent in *G. breve*. Although the ring systems in the middle of the molecules differ somewhat, type 1 and type 2 toxins share a lactone in the A ring (“head”) and a conserved structure on the “tail” ring, both of which are required for their toxic (26). Type 2 congeners are more flexible (38 rotatable bonds) than those with the type 1 backbone (31 rotatable bonds), which may play a role in their generally greater potency (27).

Brevetoxins bind with high affinity ( $K_d$  1-50 nM) to site 5 on the voltage dependent sodium channel (28). Binding to this site both alters the voltage sensitivity of the channel, resulting in inappropriate opening of the channel under conditions in which it is normally closed, and inhibits channel inactivation, resulting in persistent activation or prolonged channel opening. The toxic potency of brevetoxin congeners correlates well with their relative binding to the sodium channel (29). Backbone flexibility may determine the relative ease with which the toxin can intercalate between transmembrane domains of the sodium channel to interact with both the voltage sensor, near the “outside” of the channel and the inactivation gate on the intracellular side (30). The symptoms of NSP include nausea, tingling and numbness of the perioral area, loss of motor control, and severe muscular ache. Unlike PSP, NSP has not been known to be a fatal intoxication, with symptoms generally resolving within a few days. Like PSP, there is presently no antidote for NSP.

Unlike most other dinoflagellates responsible for seafood poisonings, *G. breve* is an unarmored dinoflagellate, which is easily lysed in turbulent water. *G. breve* red tides are frequently associated with massive fish kills. The extreme sensitivity of fish to the Florida red tide may result from lysis of cells passing through the gills. One route of human intoxication results from the consumption of shellfish that have accumulated brevetoxins by filterfeeding. Recent studies in the greenshell mussel demonstrate that brevetoxins can be metabolized by shellfish to yield novel derivatives (31).

An additional route of human exposure to brevetoxins is through respiration of aerosolized toxin, which is the result of cells breaking due to wave action. A common symptom associated with exposure to aerosolized brevetoxin is irritation and burning of the throat and upper respiratory tract. In 1996 at least 149 manatees died during an unprecedented epizootic in Florida concurrent with a persistent red tide. Immunohistochemical staining of tissues from affected animals revealed brevetoxin immunoreactivity in lymphocytes and macrophages associated with inflammatory lesions of the respiratory tract and with lymphoid tissues (32). Molecular modeling studies have implicated brevetoxin as an inhibitor of a class of lysosomal proteases, the cysteine cathepsins, which are important in antigen presentation (33). The demonstration of brevetoxin immunoreactivity in lymphoid tissue of the manatees raises the possibility of immunosuppression as a second mode by which brevetoxin exposure may affect human health, particularly in individuals with chronic exposure to aerosolized toxin during prolonged red tide incidents.

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